Impact of the prior knowledge on the quantification of in vivo \(^{13}\)C spectra using two different algorithms: LCModel and AMARES

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Introduction:
Measurements at high magnetic fields combined with improvements in localization techniques and with excellent shimming have led to important gains in sensitivity and spectral resolution of \(^{13}\)C in vivo spectra. Consequently, the amount of information that can be obtained from in vivo \(^{13}\)C spectra has considerably increased (i.e. signals from different carbon positions combined with a fine structure arising from \(^{13}\)C-\(^{13}\)C J-couplings). In this context, the quantification of in vivo \(^{13}\)C spectra becomes more challenging. Incorporation of prior knowledge has been shown to improve quantification, especially in the presence of overlapping signals. However, fitting the signals arising from different carbon positions with singlets and neglecting the multiplets due to \(^{13}\)C-\(^{13}\)C J-couplings might lead to substantial errors in the quantification of the time courses which would consequently lead to errors in the estimated metabolic fluxes. The purpose of the present study was to assess the impact of the prior knowledge on the quantification of in vivo \(^{13}\)C spectra using two different algorithms: LCModel (1, 2) and AMARES (3) and to compare the two algorithms.

Methods:

Experimental: Localized \(^{13}\)C spectra were acquired on Sprague-Dawley rats (n=4, ROI=5x8x8mm\(^3\)) fasted overnight and artificially ventilated. The femoral artery and vein were catheterized for monitoring blood gases, blood pressure, glucose concentration, and for infusion of \(\alpha\)-chloralose and glucose. An exponentially decaying bolus of 99%-enriched [1,6-\(^{13}\)C\(_2\)] glucose was administrated over 5 min, followed by a continuous infusion of 70%-enriched glucose for the remaining 6h (4). Glucose was infused at a rate adjustable to the concomitantly measured plasma glucose concentrations to maintain the desired glycaemia levels (around 300 mg/dl). All data were acquired on a 9.4T system (Varian/Magnex Scientific) using: a home-built 10mm \((^{13}\text{C})\text{mM}\) (1H quad) surface coil as RF transceiver, and the semi-adiabatic DEFT polarization transfer sequence (TR=2.5s, interpulse delay 3.8ms \((J_{\text{iso}}=130Hz)\), 45° for last \(^1\)H pulse to simultaneously measure signals from CH\(_2\), CH\(_3\), CH\(_3\) groups) (4). Field homogeneity was adjusted using FASTMAP (5).

Data analysis: In vivo \(^{13}\)C spectra were quantified using four approaches (1\(^{st}\) approach based on LCModel and the approaches 2 to 4 based on AMARES):

1) LCModel combined with a basis set generated using Matlab by simulating each isotope with the appropriate chemical shift and J-coupling pattern, as previously described by ref (2); (blue and red dots in Fig1a)

2) AMARES combined with improved prior knowledge, which was identical with that used by LCModel in our previous approach (isotopomers with the same chemical shift and J-coupling pattern). The following constraints were used: linewidths \((\leq 8Hz)\), \(^{13}\)C singlet linewidths typically obtained in our study, relative phases (fixed to zero) and Lorentzian lineshape; (green and yellow dots in Fig1a,b,c)

3) AMARES combined with minimal prior knowledge: each resonance at a specific carbon position was fitted using a singlet without any information on the J-coupling pattern (for example the multiplet of Glu at the position 4 was fitted using only one singlet). The following constraints were used: linewidths \((\leq 8Hz)\), relative phases (fixed to zero) and Lorentzian lineshape; (dark blue and pink dots in Fig1b)

4) AMARES with minimal prior knowledge as for the approach 3 with the difference that no constraints on the linewidths were imposed; (light blue and pink dots in Fig1c)

Results:
First we compared the in vivo time courses obtained with LCModel (1\(^{st}\) approach, blue and red dots in Fig1a) to those obtained using AMARES with improved prior knowledge (2\(^{nd}\) approach, green and yellow dots in Fig1a). The results of this comparison are plotted in Fig 1a. As can be seen from the in vivo time courses of Glu C4 and C3, the two approaches gave consistent and highly similar results. Therefore, in a second step we compared only the three approaches based on AMARES (Fig 1b and c) and Fig 2). In Fig 1b and c we compared the time courses obtained with the 3\(^{rd}\) and 4\(^{th}\) approach to those obtained with the 2\(^{nd}\) approach, respectively. When neglecting the multiplet structure by fitting the resonances of each carbon position by a singlet with constrained linewidth \((\leq 8Hz)\) (3\(^{rd}\) approach, dark blue and pink dots in Fig1b) the time courses for each resonance are underestimated (~40%), due to the limited prior knowledge used in AMARES (Fig1b and c). Moreover, when fitting the in vivo data with AMARES with minimal prior knowledge and without constraints on linewidths (4\(^{th}\) approach, light blue and pink dots in Fig 1c), a larger variation of the fitted data was noticed together with an underestimation of Glu C4 (~10%) and an overestimation of Glu C3 (~20%) (Fig1c). The overestimation of Glu C3 when no constraints are imposed on the linewidths (4\(^{th}\) approach) leads to a more accurate and reliable quantification of in vivo \(^{13}\)C spectra. In contrary, when limited prior knowledge is used the results obtained with AMARES are over/underestimated.

References:

Fig.1: Representative in vivo time courses of Glu C4 and Glu C3 obtained using the 4 approaches. a) 1\(^{st}\) approach (blue and red dots) vs 2\(^{nd}\) approach (green and yellow dots); b) 3\(^{rd}\) approach (dark blue and pink dots) vs 2\(^{nd}\) approach (green and yellow dots); c) 4\(^{th}\) approach (light blue and pink dots) vs 2\(^{nd}\) approach (green and yellow dots).

Fig.2: Representative fit of in vivo Glu C4 (128 averages) with AMARES and the 2\(^{nd}\) approach-improved prior knowledge, the 3\(^{rd}\) approach-minimal prior knowledge with constraints on linewidths and the 4\(^{th}\) approach-minimal prior knowledge with no constraints on linewidths.